REMARKS

The Office Action mailed September 29, 2009 has been carefully considered. Reconsideration in view of the following remarks is respectfully requested.

Rejection(s) Under 35 U.S.C. §103(a)

Claims 1-9, 12, 13 & 17 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over O'Lear et al. (U.S. pat. no. 5,252,486) and further in view of Pollema et al. (U.S. pat. no. 5,849,592).

As to claim 1, the Examiner states that O'Lear describes:

> [a] reaction loop [41] forming a transparent pipe (e.g., flow-through cell, C12/L68 & C13/L2) with a length between 0.5 cm and about 10 cm (0.5 to 2 cm, C11/L47), with which detection means (e.g. colorimeter, Fig. 1 (49), C12/L68) are coupled, ...

(Office Action at 3.) However, the Examiner is combining two components of O'Lear and conflating the properties of each component. The Examiner states that the "reaction loop" of O'Lear corresponds to item 41. (*Id.*) However, item 41 is not disclosed as being a "transparent pipe," nor is it between about 0.5 cm to about 10 cm. Rather, item 41 is taught as being "of sufficient length to allow the required residence time of about 16 minutes for the reaction mixture (col. 12, ll. 57-59), which one would expect to be far longer than 10 cm. In fact, O'Lear's preferred embodiment and Figure 1 disclose that such a 16 minute residence time would be accomplished by a coil 1000 cm long (col. 14, ll. 41-44; Fig. 1), which is 100 times longer than the maximum length specified in claim 1. Although one might plausibly assume that the colorimeter 49 contains at least a transparent window, colorimeter 49 is not part of the reaction loop, and is certainly not within the first 10 or so centimeters of the reaction loop. Rather, the transparent section comes after the 1000 cm of reactor, followed by 15 cm of tubing 43, an air filter 45, and 40 additional cm of tubing 47. The calorimeter 49 is so far separated from the reaction loop, and especially the first 10 cm of the reaction loop, that one may not reasonably consider the reaction loop to be an obvious variation of "transparent pipe with length between 0.5 cm and about 10 cm."

In anticipation of the Examiner's argument, on the other hand, that disregards reaction loop 41 and asserts that calorimeter 49 is itself the reaction loop, that would also be incorrect, as O'Lear does not describe any suitability within the colorimeter for containing a reaction, or any reason why a reaction within the colorimeter might even be desirable—it is not a reaction loop.

Indeed, O'Lear teaches that the colorimeter is not itself suitable for containing a reaction. In O'Lear, any reaction that occurs in the loop 41 must first pass through the "air filter 45 to remove any air bubbles which have unexpectedly evolved during the reaction heating" (col. 12, ll. 62-62). As O'Lear states, "The evolution of gas bubbles can cause unacceptable detector 'noise' when the reaction mixture containing the color complex is passed through the colorimeter for reading" (col. 11, ll. 24-27). Thus, the transparent reaction loop of claim 1, which contains no air filter after the reaction and prior to the colorimeter zone (which in the case of claim 1 are not distinguished from each other), is taught by O'Lear to be "unacceptable."

Furthermore, O'Lear teaches that it is necessary "to reduce the temperature of the reaction mixture prior to passing it through a colorimeter" either by employing a cooling loop as in the prior art, or by using an air filter as disclosed in O'Lear (col. 11, ll. 31-38). Thus, the reactor loop of claim 1 would be unacceptable under the teachings of O'Lear, as there is no method for reducing temperature or pressure between the reactor loop and the colorimeter.

The teachings of O'Lear are incompatible with advantages of claim 1, which uses a comparatively short, transparent reaction tube which makes it possible to use the system on microfluidic chips and, for example, makes possible the creation of space and time plots along the length of the transparent tube (Application, p. 9, ll. 1-13). This is impossible in O'Lear, where the reactor loop is long enough that the reaction is expected to come essentially to completion by the time it reaches the colorimetric detector 49, a result O'Lear considers desirable (col. 4, ll. 29-31).

Pollema contributes nothing to remedy these deficiencies in the O'Lear reference. (*See* discussion below.) Pollema, for example, does not describe an approximately 0.5 to 10 cm transparent reaction tube, and does not teach how or why one might be used.

As to independent claim 12, the Examiner states that O'Lear discloses:

> [a] reaction loop (e.g. coil of tubing, Fig. 1 (41), C12/L57-58) . . . wherein the reaction loop consists of a transparent pipe (e.g., flow-through cell, C12/L68 & C13/L2) and the outlet of which is connected to the transparent pipe with a length between about 0.5 cm and about 10 cm (0.5 to 2 cm, C11/L47) . . . .

(Office Action at 6.) Again, for the reasons described above, the Examiner is combining two components of O'Lear and conflating their properties. In claim 12 of the present application, "the reaction loop consists of the transparent pipe" which has "a length between about 0.5 cm and about 10 cm." In O'Lear, however, the reaction loop 41 does not even contain a transparent pipe, and it is far longer than 10 cm. Far downstream of the O'Lear reaction loop, past the air

filter, there may be a transparent window as part of the colorimeter, but it is separated from the reaction loop by an air filter and by long lengths of tubing, and it is not part of the reaction loop. For all the reasons discussed above with respect to claim 1, neither O'Lear nor Pollema, nor their combination describes the system of claim 12.

Claims 2-11 and 13-17 variously depend, directly or indirectly, from the base claims 1 and 12 addressed above. Pollema fails to remedy the above-mentioned shortcomings of O'Lear with respect to the base claims. Accordingly, claims 2-11 and 13-17, which by definition include all the limitations of the base claims, are patentable over the combination of these references.

In addition, the Examiner states, regarding dependent claim 2, that O'Lear discloses that "a concentration gradient is detected in the reaction loop (see determination of concentration at designated intervals, C4/L9-22)" (Office Action at 5). However, O'Lear does not describe reading of colorimetry values at designated intervals. It is sampling of the test specimen that occurs at designated intervals, and each time this sampling occurs, it is injected into the reaction loop and the concentration is measured. O'Lear does not refer to measurement of a concentration *gradient*, just the actual concentration of each sample which is injected at periodic intervals.

Further, the Examiner states, regarding dependent claim 9, that O'Lear discloses that "linear detection (e.g. colorimeter, Fig. 1 (49), C12/L68) is performed along the reaction loop." However, O'Lear provides no disclosure sufficient to teach or suggest the production of a space and time plot of the reactions in a transparent reaction loop. O'Lear does not teach or suggest that within the colorimeter, there may be different readings at different points along the length of the calorimeter. Indeed, given the long 16 minute residence times in the O'Lear apparatus, the fact that the reaction loop is far longer than the sensing window of the colorimeter, and the fact that by the time the samples reach the colorimeter, the reaction has essentially gone to completion, there would be no need to measure optical properties as they might differ along the length of a transparent tube.

Therefore, because O'Lear and Pollema, either separately or in combination, fail to disclose or teach all the limitations claims of claims 1-9, 12, 13 & 17, the Examiner's rejection under 35 U.S.C. §103(a) fails to rise to the level of a *prima facie* case of obviousness, at least for the reasons outlined above. Accordingly, it is respectfully urged that the obviousness rejection of claims 1-9, 12, 13 & 17 is improper and should be withdrawn.

Claims 1, 2, 9, 12 & 16 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Pollema et al. (U.S. pat. no. 5,849,592). According to the Examiner, although Pollema does not disclose the use of a "T-shaped branch," Pollema discloses "a various required connecting tubing used (C1/L51-52)," that "[i]t is well known in the art that the connections can have a variety of shapes and configurations, including T-shaped," and that "[t]he change in configuration of shape of a device is obvious absent persuasive evidence that the particular configuration is significant." (Office Action at 11.)

However, the presence of a T-shaped branch is more than just an arbitrary design choice in selecting tubing. Rather, it is an unobvious part of the injection method, with unobvious improvements over the prior art including Pollema. Pollema is an example of carrier-less sequential injection analysis (CSIA) described from page 5, lines 3-27. It uses a multi-position valve (MPV), a holding coil (HC), and a bi-directional pump to sequentially load reagents into the stream containing the analyte. However, it is typically undesirable to use the valve and bi-pump scheme of Pollema when the process is miniaturized. Valves in microfluidic circuits require an additional non-trivial technological step, and bidirectional microfluidic pumps pose other concerns such as the difficulty of degassing when bubbles form. (Application at 7, ll. 17-28.) Thus, Applicants have made an unobvious and significant contribution to the art by eliminating the necessity of a valve, holding coil, or bidirectional pump. Applicant's design can be a much simpler design and more appropriate for microfluidic circuits. The use of a T-shaped branch means that no valves need to be opened, closed, or turned at the mixing point. Furthermore, this particular design means that there is no longer a need for a bidirectional pump to load reagents and analytes in a manner suitable for reaction and later analysis.

In addition, the Examiner argues in response to Applicants' earlier argument that Pollema does not disclose the claimed length of the reaction loop, that "since the instant specification is silent to unexpected result, it would have been obvious to one having ordinary skill in the art at the time the invention was made to vary the length of the pipe to control liquid volume in the system, see C1/L43-58 & C2/L44-45." (p. 17). However, the Specification is not silent on that point. Rather, it argues that the Pollema CSIA system:

> cannot be used [in microfluidic chips] not only because of [its] large consumption of fluids in general, but also because of the size of the volumes and lengths of the retaining and reaction loops, the difficulty in making them compatible with the constraints required by most methods for manufacturing miniaturized circuits."

(Specification at 7, ll. 11-16.) In fact, the Pollema system consumes a large amount of fluids, partly because it requires a voluminous holding coil (HC) and reaction coil (RC). Pollema teaches that the holding coil (HC) "serves as the method of separating the old from new sample" (col. 4, ll. 63-64). A bidirectional pump means that the HC is repeatedly contaminated by reactants, and must be flushed by excess analyte. To avoid contamination, Pollema teaches that the HC must have "an appropriate volume" (col. 5, l. 17). In fact, the HC "volume should be maximized to create the largest possible zone of defined sample" (col. 5, ll. 35-37). This is not a problem for the instant Application, which does not require a multiposition valve, bidirectional pump, and holding coil, replacing these elements instead with a T-shaped branch configuration.

Further, the Examiner argues that Pollema describes a "reaction loop (e.g. reaction coil, Fig. 4A (RC), C4/L49) sample forming a transparent pipe with which detection means (e.g. flow-through detector, Figs. 1-4 (D), C2/L53) are coupled" (Office Action at 9). However, Pollema does not disclose a reaction loop that forms a transparent pipe. Rather, Pollema discloses an unspecified length of reaction coil tubing in fluid communication with a separate detector D. Such a configuration does not allow the benefits and flexibility of the present disclosure, such as the ability to create plots of the reagent as it passes through the reaction loop, not just as a function of time passing by one point in a detector, but also as a function of length along the reaction loop, as the reaction is taking place.

Thus, for the above reasons, Pollema does not disclose or teach all the limitations of independent claims 1 and 12, nor are those limitations obvious in view of the prior art. Certainly, the reaction loop in Pollema does not "consist[] of a transparent pipe" as required by claim 12.

Claims 2-11 and 13-17 variously depend, directly or indirectly, from the base claims 1 and 12 addressed above. Accordingly, claims 2-11 and 13-17, which by definition include all the limitations of the base claims, are patentable over Pollema. Additionally, Pollema does not disclose the detection of a concentration gradient as required by claim 2. Although the Examiner cites "C1/L25-27" of the patent on that point (Office Action at 11), this merely refers to the scientific fact that such a gradient exists. Pollema does not disclose how to measure or detect it in accordance with the Pollema invention.

Further, the Examiner argues that linear detection, as required by claim 9, is disclosed in Pollema claims 5 and 6 (Office Action at 11). However, these Pollema claims merely refer to use of a "colorimeter" and a "potentiometer," which does not imply linear detection in order to

obtain a space and time plot. A linear detection requires measurement at multiple points in space, and the instruments disclosed in Pollema are not taught as anything other than stationary instruments measuring concentration at one point in the flow stream.

Conclusion

In view of the preceding discussion, Applicants respectfully urge that the claims of the present application define patentable subject matter and should be passed to allowance.

If the Examiner believes that a telephone call would help advance prosecution of the present invention, the Examiner is kindly invited to call the undersigned attorney at the number below.

Please charge any additional required fees, including those necessary to obtain extensions of time to render timely the filing of the instant Amendment and/or Reply to Office Action, or credit any overpayment not otherwise credited, to our deposit account no. 50-3557.

Respectfully submitted,
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